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(54) Stable preparation containing azelastine hydrochloride.

(57) To provide a stable peparation which does not produce cystalline hydrates, by making a preparation containing azelastine hydrochloride and a fatty acid of 8 or more carbon atoms, as well as an azelastine hydrochloride preparation of the same composition as the above which has excelent percutaneous and mucosal absorbability.

A fatty acid of 8 or more carbon atoms is added to azelastine hydrochloride and adjusted to a pH of 6 to 9. For an increase in the percutaneous absorbability, 1, 2 or more ingredients selected from the group consisting of ethanol, isopropanol and polyhydric alcohols are included therein, and for preparations an apropriate amount of lecithin is included optionally.

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The present invention relates to a stable preparation containing azelastine hydrochloride and a medicinal preparation incorporating it which has excellent percutaneous and mucosal absorbability.

Azelastine hydrochloride has been used as an anti-allergy drug in medicinal treatments for bronchial asthma, allergic rhinitis, hives, eczema, dermatitis, atopc dermatitis, cutaneous pruritus, prurigo, etc.

Generally, the abdorption of basic medicines is thought to be high for non-dissociation typed and low for dissociation tipes. For example, in Drug Metaboslism Review 8(2), 223-23, 1978, it is shown that the percutaneous penetration speed of the basic medicine scopolamine is in direct proportion to pH, and thus since azelastine is a basic medicine, its absorption may also be expected to be favorable in direct proportion to the pH of the preparation.

However, since the acid dissociation constant (pKa) of azelastine is approximately 9.5 and thus to make the proportion of non-dissociation type molcules 50%, it is necessary to adjust the pH of the preparation to 9.5, differing vastly from the physiological pH of skin and membranes.

Further in the aqueous preparation, the non-dissociation type molecules of azelastine form crystalline hydrates of poor solubility, causing precipitation, even if the pH and eventually the proportion of the non-dissociation type molecules is increased, and therefore it is difficult to obtain a homogeneous preparation of azelastgene.

In order to prevent precipitation of crystals in the preparation, past known methods habe included adding solents in which the crystals are easily soluble, or adding a surface active agent to solubilize the non-dissociation type medicine, or adding a water soluble polymer to suppress crystal growth.

Also, publicly known techniques of raising the percutaneous absorbability of azelastine hydrochloride habe been preparted in Japanes Patent publication (Kokai) Hei 2-288827 and Japanese Patent Application SHO 63-278108. The former is charcterized by the additional of an alkylglycerine to the preparation, and the later is characterized by incorporation of a lactic acid ester of an aliphatic alcohol, such as, for example, cetyl lactate, myristyl lactate, lauryl lactate, and/or a fatty acid monoglyceride of 8 to 12 carbon atoms.

Further, in Japanese Patent publication (Kokai) Sho 61-254532, a method is disclosed wherein a cationic water soluble medicine and an acidic oil soluble substance are combined to increase the percutaneous absorbabilty of the medicine. Another known general method for increasing the percutaneous and mucosal absorbability enlarges the amount of the main ingredient by maximizing its thermodynamic activity in the base.

As describes preciously, the producing of crystalline hydrate of azelastine gives rise to such a unpreferred problem that the content of azelastine is heterogenoeus, the absorbability of medicine is lowered and the crystal thereof is changed into an unpreferred form during adminstration.

Also, azelastine hydrochloride has a low solubility in solvents which may be used as drugs, and thus precipitaton of crystals cannot be prevented by addition of a solvent. In order to prevent the production of hydrates by additon of a surface active agent it is necessary to use it at a high concentration in the mixture, which can cause irritation of the skin or membrane. Further, it was not possible to suppress the production of hydrates of azelastine hydrochloride through the addition of a water soluble polymer. The alkylglycerine disclosed in Japanese Patent publication (Kokai) Hei2-288827 are not commercially available and are difficult to obtain.

With the technique disclosed in Japanese Patent publication (Kokai) Sho 63-278108, when the amount of azelastine hydrochloride is high compared to the base, there is a marked improvement in the percutaneous absorbability thereof, but when the amount is low the azelastine hydrochloride disperses in the base, causing the disadvantage of poor percutaneous absorbability. Azelastine hydrochloride is a cationic drug, but no increase in absorbability was observed with the technique disclosed in Japanese Patent publication (Kokai) Sho 61-254532.

Also, if the amount of the drug in the base is increaed with consideration to the solutiblity of the drug in the base, it is easy to increase the percutaneous absorbabiltiy, but the many disadvantages in such a case include a rise in production cost, an increase in the danger of misusage of the preparation, and irritation of the skin due to the drug. The inventors of the present invention carried out diligent research to ovecome the above mentioned disadventages, and succeeded in finding a solution through the method described below, by which the present invention was completed.

That is, the present invention relates to a preparation containing azelastine hydrochloride and a fatty acid of 8 or more carbon atoms. It further relates to a preparation contianing azelastine hydrochloride and a fatty acid of 8 or more carbon atoms, as well as 1, 2 or more ingredients selected from the group consisting of polyhydric alcohols, ethanol, isopropanol and lecithin.

The amount of azelastine hydrochloride is not limited, but an amount should be use which is necessary to exhibit the desired pharmacological effect, and that amount is betwen 0.001% and 2% by weight of the preparation. Amounts less than this will not provide an adequate pharmacological effect, and amounts

greater than this are thought to be economically disadvantageous.

The fatty acid of 8 or more carbon atoms used according to the present inventon may be a saturated, unsaturated or branched fatty acids. There is no particular restriction, but the preferred carbon number of the fatty acids is from 8 to 22. If the carbon number is lower than this, there is no effect of suppression of azelastine hydrate production, and fatty acids with higher carbon numbers are difficult to obtain as materials for medicinal preparations, creating a problem for practical use. The fatty acid used according to the present invention may be a saturated, unsaturated or branched fatty acid, but it should be relatively stable and change little through time, and should cause little irritation and be highly safe when applied to the body. Preferred examples of fatty acids to achieve the object of the present invention include for example caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, isostearic acid, arachidic acid, behenic acid, palmitoleic acid, oleic acid, linolic acid, linolenic acid, linoleinic acid and erucid acid. However, polyunsaturated fatty acids themselves have low stability, and thus when making preparations thereof it is necessary to ensure the stability by, for example, the addition of an antioxidant. More preferable fatty acids for incorporation in the preparation include capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, isostearic acid, behenic acid, oleic acid, palmitoleic acid and lipolic acid.

For stablility of the preparation, and in order to achieve the effect of the present invention, the relative amount of fatty acid to azelastine hydrochloride should be more than 0.1 parts by weight, and preferabley 0.3 to 10 parts by weight, and more preferably 0.5 to 5 parts by weight. If the amount of fatty acid is less than this, there is no effect of suppression of crysal formation of azelastine hydrate by adjustment of the pH.

If the amount of fatty acid is greater than this range, then depending on the type of fatty acid selected and the other ingredients added to the preparation, there is sometimes precipitation of fatty acid salts or a mixture of a fatty acid and a fatty acid salt (fatty acid soap), called acid soap, making it difficult to obtain a stable, homogeneous preparation as desired by the present invention.

Next, the polyhydric alcohols which may be used according to the present invention, include for example: propylene glycol, 1,3-butylene glycol, dipropylene glycol, sorbitol, maltitol, glycerine. Ethanol, isopropanol and polyhydric alcohols may be used in amounts which uniformly dissolve the above mentioned fatty acid and azelastine hydroxide, as well as lecithin. The amount of alcohol and/or polyhydric alcohol added is not particularly restricted, but should be 0.5 to 50 parts by volume, and preferably 0.5 to 30 parts by volume of the preparation.

Being economical and easy to obtain, lecithin from egg yolks or soy beans may be used as the lecithin. Also, from the point of view of color and smell of the raw substance, a hydrogenated one is preferable, though a unhydrogenated type may of course be used. Further, commercially available synthesized lecithin (phosphatidyl choline) may be used. The amount of lecithin added is not particularly resticted, but should be in a ratio of 0.01 to 5 parts by weight, and preferalby 0.02 to 2 parts by weight to 1 part by weight of azelastine hydrochloride.

The pH of the preparation according to the present invention should be adjusted to a physiological acceptable value of between 6 and 9. The pH of the preparation was measured by adding pure water to the prepartion for a 10% suspension. If the pH is lower than this, almost all of the azelastine is thought to exist in a state of dissociation, and this is disadvatageous from the point of view of absorption of the drug. Also, depending on the type and amount of fatty acid to be incorporated and the composition of the preparation, there is sometimes precipitation of fatty acid or acid soap crystals, making it difficult to achieve the object of the present invention. If the pH is higher than this range, the ingredients incorporated in the preparatation may be decomposed and there may be coloration of the preparation, making it unsuitable as a medicinal preparation.

Concrete dosage forms of the preparation according to the present invention include liquid agents, such as for example eye drops, nasal dops, lotions, syrups and sprays, semi-solid preparations such as for example oinments, creams, gels, tapes and paps, and solid agents such as for example suppositories. In addition to the above mentioned ingredients, these preparations may be made with other ingredients generally used as raw materials in medicinal preparations.

The ingredients used may be for example animal or vegetable oils (soy bean oil, beef tallow, synthesized glyceride, etc.), ester oils (octyldodecyl myristate, isopropyl myristate, etc.), higher alcohols (cetostearyl alcohols, behenyl alcohols, etc.), silicon resins, silicon oils, surface active agents (for example polyoxyethylene fatty acid esters, sorbitan fatty acid esters, glycerine fatty acid esters, polyoxyethylenesorbitan fatty acid esters, polyoxyethylene hydrogenated castor oil, polyocyethylene ployoxypropylene block copolymers), alcohols (for example ethanol, isopropanol), polyhydric alcohols (for example glycerine, propylene glycol, dipropylene glycol, sorbitol), sugars (for example glucose, sucrose), inorganic powders (for example silicic acid anhydride, magnesium aluminum silicate, aluminum silicate), purified water. For

adjustment of the pH, inorganic acids (for example hydrochloric acid, phosphoric acid), alkali metal salts of inorganic acids (for example sodium posphate), inorganic bases (for example sodium hydroxide), organic acids (for example lower fatty acids, citric acid, lactic acid), alkali metal salts of organic acids (for example sodium hydroxide), organic acids as for example lower fatty acids, citric acid, lactic acid), alkali metal salts of organic acids (for example sodium citrate, sodium lactate), organic bases (for example arginine, ethanolamine) may be used. Also, if necessary presentatives, anti-oxidants, may be added.

A preparation using the ingredients listed above may be produced according to any generally used method. An explanation will be given below of an example of a method for the production of a gel ointment. Azelastine hydrochloride, fatty acid and lecithin are measured out, and 1 or more ingredients selected from the group consisting of ethanol, isopropanol and polyhydric alcohols are addeed thereto, each ingredient is uniformly dissolved, and 0.1 N sodium hydroxide is added to prepare a solution. Separately, a Miktsuya Kako product called Carbopol (carboxyvinyl polymer) is dissolved, sodium hydroxide is used to adjust the pH of the gel to 8, and the pro-preapared solution is added thereto with adequate stirring to obtain a uniform gel ointment.

According to the present invention, the mechanism of suppression of the production of azelastine hydrate is not clear, but since such effect is not exhibited with the adition of acids of small carbon numbers, such as acetic acid, propionicacid, butrylic acid, it is supposed that it is due not to a simple salt-exchange, but to a complicated interaction between each of the ingredients.

A more concrete explanation will be made of the present invention with reference to examples given below, which should not be elucidated as limitations thereto.

Example 1 (Lotion)

0.3 g of azelastine hydrochloride, 0.28 g of myristic acid and 10 ml of ethanol were measured out, heated and dissolved. The solution was added to purified water, and the pH was adjusted to 7.5 with sodium hydroxide to obtain a translucent lotion.

Example 2 (Lotion)

0.3 g of azelastine hydrochloride, 0.28 g of myristic acid (Nippon Yushi Co.) and 0.1 g of lecithin (refined soy beans lecithin, Ajinomoto Co.) were weighed out, and 15 ml of ethanlol was added thereto, and the mixture was heated to prepare a solution. The solution was added to purified water which contained 12 ml of 0.1 N sodium hydroxide, and more purified water was added to make 100 ml. In this manner, a lotion with pH 8 and containing 0,3% azelastine hydrochloride was obtained.

Example 3 (Gel ointment)

0,3 g of azelastine hydrochloride, 0,5 g of oleic acid and 0,2 g of lecithin (PC-70, Nissei Seiyu Co.) were weighed out, 5 g of propylene glycol and 5 g of ethanol were added hereto and dissolved, and 9 g of 0.1 N sodium hydroxide was added to the solution. This was then added to 80 g of a gel containing 0.6 g of Carbopol 940 and purified water, and whose pH had been adjusted to 8 with sodium hydroxide, and adequate stirring was done for homogenity. In this manner, a gel ointment with pH 8 and containing 0.3% azelastine hydrochlorid was obtained.

Example 4 (Cream)

3 g of stearic acid, 15 g of squalane SKR, 8 g of cetostearyl alcohol, 1 g of propylene glycol monostearate, 1 g of clycerine monostearate and 1 g of polyoxyethylenesorbitan monostearate (Nikol TS-10), Nikko Chemicals Co.) were weighed out and heated to prepare a solution. Then 1.0 g of azelastine hydrochloride, 0,3 g of hydroxyethyl celulose, 2 g of dipropylene glycol, 3 g of glycerine (Japanese Phamacopeia), 1.7 g of disodium hydrogen phosphate, and an appropriate amount of water were weighed out and heated to prepare a solution. Both solutions were mixed and stirred, 11 ml of 0.1 N sodium hydroxide was added thereto, and the mixture was cooled while stirring at room temperature. In this manner, a cream with pH 7,5 and containing 1% azelastine hydrochloride was obtained. The pH of the cream was measured for a 10% suspension in purified water.

Example 5 (Ointment)

0.1 g of azelastine hydrochloride, 0.1 g of lauric acid, 2 g of dipropylene glycol and 3 g of glycerine monooleate were weighed out and heated to prepare a solution. To this was added Plastibase 50W (Nippon Sukuibu Co.), and the mixture was adequately stirred. Then 0,45 ml of 1 N Sodium hydroxid was further added thereto, and the mixture was well stirred for homogenity, to obtain an ointment containing 0.1% azelastine hydrochloride. This ointment was to 10% suspended in water, and after heating and stirring the pH of the water phase was measured to be 7.5.

Example 6 (Lotion)

0.3 g of azelastine hydrochloride and 0.3 g of oleic acid (Extra oleic 90, Nippon Yushi Co.) were weighed out, 16 ml of 0.05 N sodium hydroxide was added thereto, and the mixture was stired and dissolved. To the resulting solution was added 5 g of propylene glycol and purified water was added to 10 ml to obtain a lotion containing 0.3% azelastine hydrochloride.

Example 7 (Eye drops)

0.05 g of azelastine hydrochloride, 1 g of propylene glycol and 0.05 g of myristric acid wre weighed out and heated to prepare a solution. To the solution was added 1,37 ml of 0,1 N sodium hydroxide and then addition was made of a solution of 1 g of glycerine, 0.1 g methylparabene and 0.02 g of propylparaben in 80 ml of warm distelled water. After cooling, distelled water was added thereto to a total volume of 100 ml, and filtration was done with a 0,22 µm membrane filter to obtain an eye drop solution with pH 8 and containing 0,05 % azelastine hydrochloride.

Example 8 (Nasal drops)

0.01 g of azelastine hydrochloride, 0,01 g of lauric acid, 0,002 g of refined soy bean phospholipid, 1 ml of ethanol and 1 ml of glycerine were weighed out and heated to prepare a solution. Then 80 ml of purified water, 0,15 g of methylparaben and 0,2 g of hydroxyethyl cellulose were heated to prepare a solution, and 0,7 ml of 0.1 N sodium hydroxide was added thereto. Both solutions were mixed and stirred and purified water was added to a total volume of 100 m to obtain a nasal drop solution with pH 7.5 and containing 0.01% azelastine hydrochloride.

Example 9 (Syrup)

0.2 g of azelastine hydrochloride, 0.1 g of stearic acid, 0.1 g of myristic acid, 0,05 g of polysorbate 80, 0,5 g of ethanol, 3 g of glycerine and 6 ml of 0.1 N sodium hydroxide were weighed out and heated to prepare a solution. Then 35 g of sucrose, 5 g of D-sorbit, 0,15 g of methylparabene, 0.05 g of propylparabene and an appropriate amount of fragrance were added thereto, and purified water was added to make 100 ml.

Example 10 (Suppository)

0.5 g of azelastine hydrochloride, 0.8 g of lauric acid, 0.5 g of triethanolamine, 2 g of glycerine (Japanese Pharmacopeia) and 1.5 g of glycerine monooleate were weighed out and heated to prepare a solution, which was then added to 94.7 of a melted suppository base (Wettezol H15R), mixed, poured into a suppository mold and cooled to obtain a suppository containing 0.5% azelastine hydrochloride.

Experiments (Azelastine hydrate production-suppressing effect of each of the additives)

Experiment 1

The azelastine hydrate production-suppressing effect was tested for each of the additives in azelastine hydrochloride solutions. Each of the additives were added to 0.3 g of azelastine hydrochloride, the pH was adjusted to 8 with sodium hydroxide, and purified water was added ot a total volume of 100 ml to determine whether or not azelastine hydrate crystals were produced. The identification of azelastine hydrate was done by filtering off the precipitates produced in the test solutions, drying them at room temperature, measuring

thermal analysis (TG-DTA) (Fig. 1) and IR spectrum (azelastine hydrochloride reference standard: Fig 2; azelasine hydrate: Fig. 3), and then comparing them to the standard.

Table 1 on page 19 shows the azelastine hydrate production-suppressing effect of each of the additives. Cases in which there was absolutely no hydrate formation are represented by [O], cases in which hydrate formation decreases compare to the produced water are represented by [Δ] and cases in which there was no hydrate production-suppressing effect are represented b y [x].
It is clear from table 1 that addition of fatty acids of 8 carbon atoms or greater had an azelastine hydrate production-suppressing effect.

Experiment 2

A small amount of the lotion in example 1 was packaged into glass containers, and stored in a refrigerator, at room temperature or in an inucbator at 45 °C , and sequential observation was made of the presence or absence of azelastine hydrate. The result was that no azelastine hyrates were observed to be formed during 2 month under all the above conditions.

Experiment 3

A percutaneous absorbability test was done for the preparations (Examples 1 and 5) according to the present invention.
The abdomens of 8-11-week-old hairless rats (Ishikama experimental animals) were shaved the day before the test with an electric clipper and shaver. On the day of the test, the skin was checked for cuts, they were killed with an overdose of sodium pentobarbital, and the abdomen skin was extraced. This was attached to a horizontal membrane type of percutaneous penetration experiment cell (effective penetration area 8.04 cm^2, receiver volume 46 ml) so that the epidermis was on the surface. The receiver used was an isotonic phosphate buffer solution at pH 7.4. To the donor side was added 1 ml of the preparation, the receiver solution was stirred on a water bath at 35 °C with a magnetic starrer and sampling was made thereof at determined intervals. Then high performance liquid chromtography was used to measure the concentration of azelastine in the receiver solution in terms of azelastine hyydrochloride.

Comparison 1

Purified water was added to 0.3 g of azelastine hydrochloride to make 100 ml. The pH of the solution at this time was 5.8.

Comparison 2

Purified water was added to 0.3 g of azelastine hydrochloride, adjusting the pH with sodium hydroxide, to make a total volume of 10 ml. The pH of the aqueous solution at this time ws 8.0.

Experimental results

A quantitative determination was made of the azelstine in the receive solution after 24 hours, and the amount of azelastine hydrochloride penetrated per 1 cm^2 of skin was expressed in μg. The results are shown in Table 2 on page 20. It is clear from Table 2 that the preparations according to the present invention had the maximum percutaneous penetration of azelastine.

Brief description of the figures

Fig. 1: A thermoanalysis (TG-DTA) diagram for azelastine hydrochloride and azelastine hydrate.
Fig. 2: An IR spectrum diagram for the azelastine hydrochloride reference standard
Fig. 3: An IR spectrum diagram for azelastine hydrate.

Table 1

Azelastine hydrate production-suppressing effect of each of the additives		
Additive	Amount added (%)	Effect against production of azelastine hydrates
None	-	x
Propylene glycol	30	x
HCO-60	5	x
Polyoxyethylene hydrogenated castor oil	1	x
Twin 80	5	x
Ethanol	30	x
Acetic acid	0.5	x
Propionic acid	0.3	x
Butyric acid	0.5	x
Caproic acid	0.5	x
Caprylic acid	0.5	△
Capric acid	0.5	○
Lauric acid	0.5	○
Myristic acid	0.1	△
Myristic acid	0.3	○
Myristic acid	0.5	○
Palmitic acid	0.5	○
Stearic acid	0.5	○
Isostearic acid	0.5	○
Behenic acid	0.5	○
Palmitoleic acid	0.5	○
Oleic acid	0.1	△
Oleic acid	0.3	○
Oleic acid	1.0	○
Linolic acid	0.5	○
Linolenic acid	0.5	○
Erucid acid	0.5	○

Table 2

Results of percutaneous absorbability test	
Sample	Amount of medicine penetrating 1 cm^2 of skin in 24 hours
Example 1	127
Example 5	97
Comparison 1	11
Comparison 2	41

Claims

1. A preparation containing azelastine hydrochloride and a fatty acid of 8 or more carbon atoms.

2. A preparation according to claim 1, characterized in that the fatty acid is 1, 2 or more fatty acids selected from the group consisting of caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, isosteraric acid, arachidic acid behenic acid, palmitoleic acid, oleic acid, linolic acid, linolenic acid, linoleinic acid and erucic acid.

3. A preparation according to claim 1 or 2, characterized in that the pH of the preparation is between 6 and 9.

4. A preparation containing azelastine hydrochloride and a fatty acid of 8 or more carbon atoms, as well as 1, 2 or more ingredients selected from the group consisting of ethanol, isopropanol, lecithin and polyhydric alcohols.

5. A preparation according to claim 4, characterized in that the polyhydric alcohol is 1, 2 or more polyhydric alcohols selected from the group consisting of glycerine, propylene glycol, 1,3-butylene glycol, dipropylene glycol and sorbitol.

Fig. 1 THERMOANALYSIS [TG-DTA] DIAGRAM FOR AZELASTINE HYDROCHLORIDE (A) AND AZELASTINE HYDRATE (B)

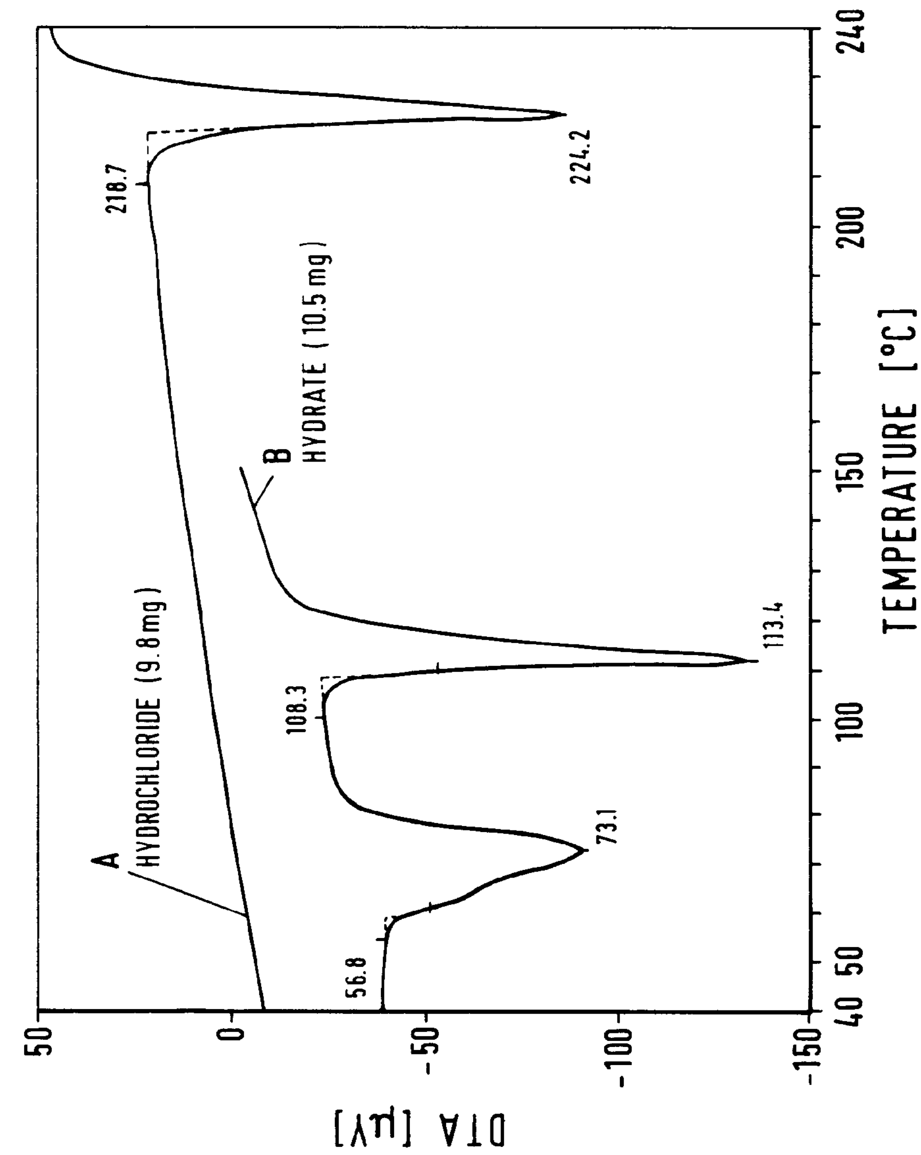


Fig. 2 IR SPECTRUM DIAGRAM FOR THE AZELASTINE HYDROCHLORIDE REFERENCE STANDARD

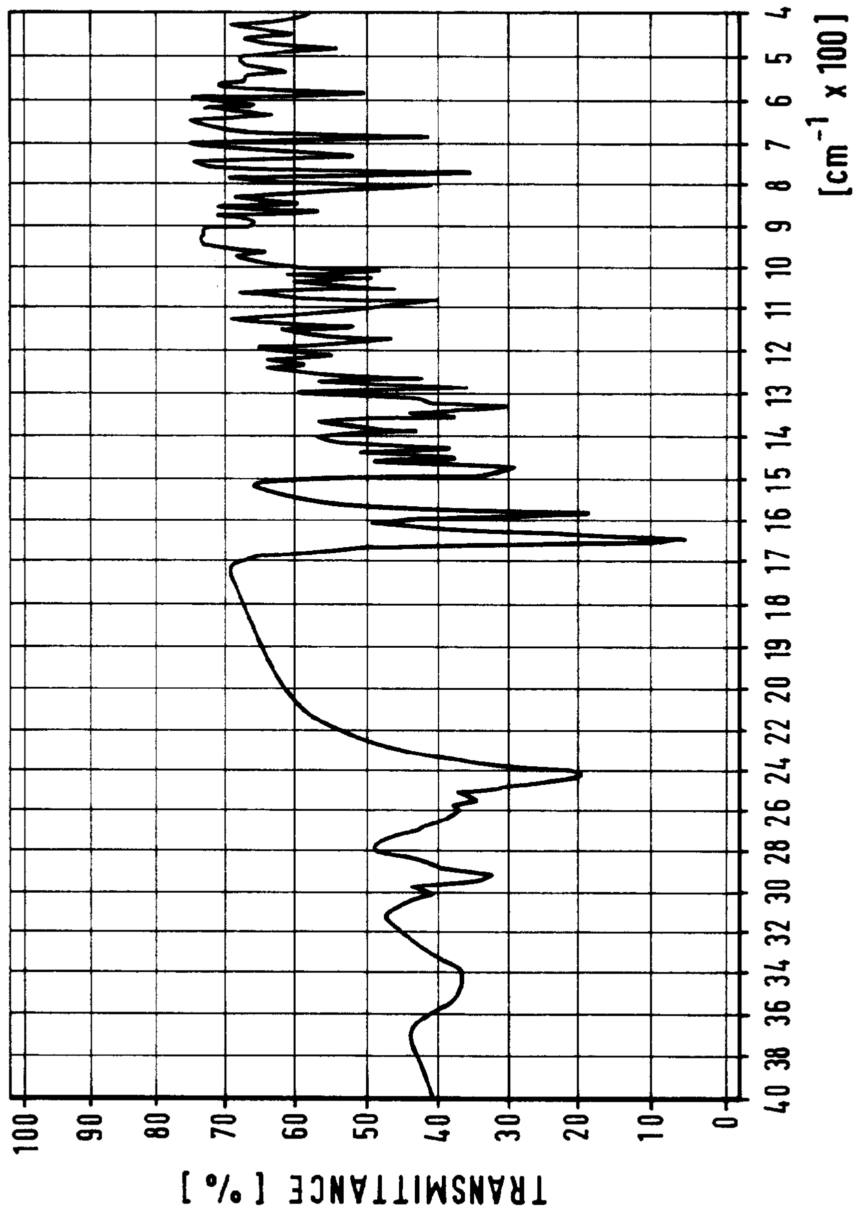
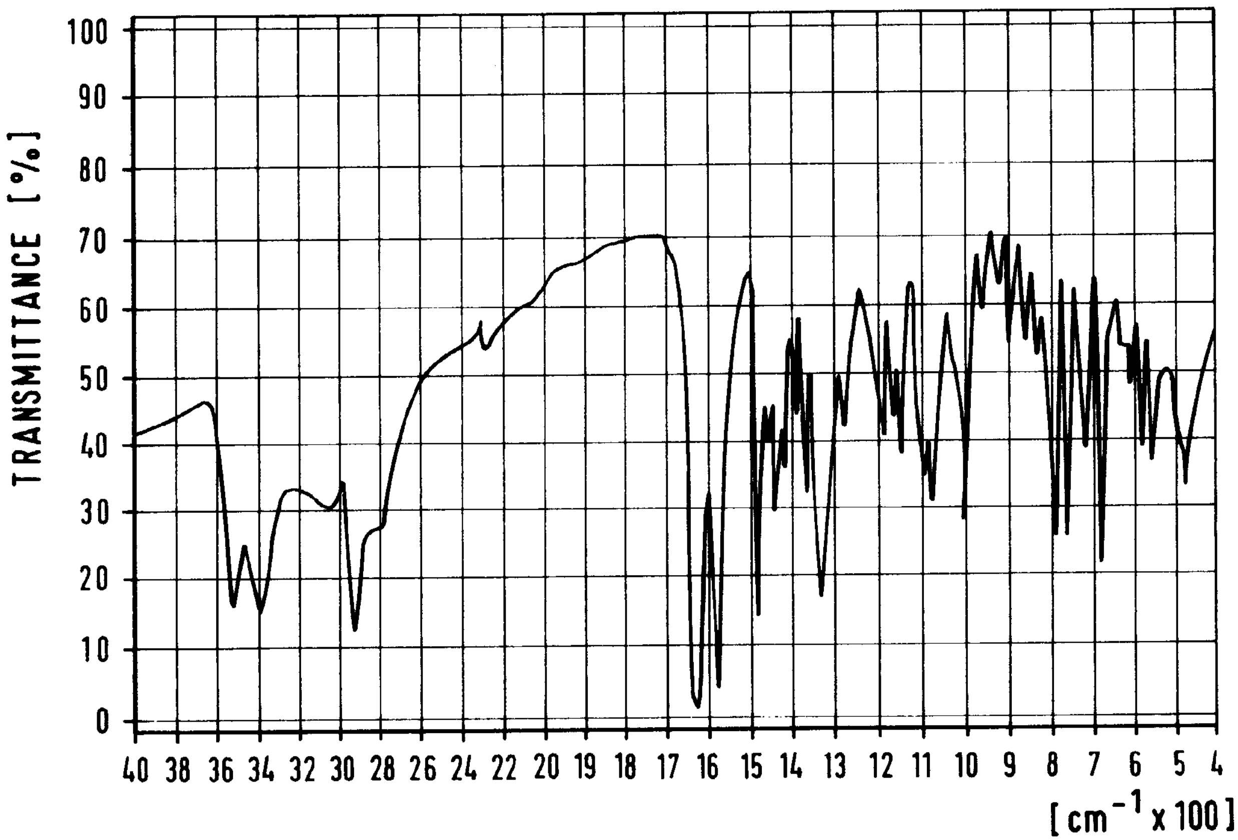


Fig. 3 IR SPECTRUM DIAGRAM FOR AZELASTINE HYDRATE



European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 93 11 1334

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	EP-A-0 378 086 (ASTA PHARMA AG) * claim 1 * ---	1-5	A61K31/55 A61K47/12
D,A	Week 9025, Derwent Publications Ltd., London, GB; AN 90-189693 & JP-A-02 124 824 (EISAI KK) * abstract * ---	1-5	
A	US-A-4 879 297 (M. MAHJOUR) * the whole document * ---	1-5	
A	EP-A-0 428 352 (LABORATORIOS BETA S.A.) * the whole document * ---	1-5	
A	EP-A-0 368 409 (NORWICH EATON PHARMACEUTICALS INC.) * the whole document * ---	1-5	
A	EP-A-0 295 411 (SANSHO CO., LTD.) * the whole document * -----	1-5	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	29 SEPTEMBER 1993	FOERSTER W.K.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
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